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Orbital myeloid sarcoma: a case report

Sarcoma Mielóide Orbitário: relato de caso

Sarcoma mieloide de la órbita: reporte de caso

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ABSTRACT

Myeloid sarcoma is a rare, extramedullary solid tumor, which is usually associated with acute myeloid leukemia (AML), and may involve various parts of the body, including the eye socket. Its diagnosis is challenging and is mainly performed by anatomopathological and immunohistochemical analyses, because imaging findings are nonspecific. The objective of this study was to report the case of a patient in remission for AML, with a history of breast cancer and neurofibromatosis type 1, which evolved with rapid proptosis in the left eye and was diagnosed as myeloid sarcoma. Subsequent tests showed no recurrence of AML. This pathology has an indeterminate prognosis, and the main line of treatment includes chemotherapy, although radiotherapy and surgery may be used in selected cases.

Keywords: Sarcoma, Myeloid; Leukemia, Myeloid, Acute; Exophthalmos.

RESUMO

O Sarcoma Mieloide é um tumor extramedular sólido, raro, geralmente associado à leucemia Mieloide aguda (LMA), podendo envolver diversas partes do corpo, incluindo a órbita. Seu diagnostico é difícil e realizado principalmente pelo anatomopatológico e imunohistoquímica, pois os exames de imagem são inespecíficos. O objetivo deste trabalho é relatar o caso de uma paciente em remissão para LMA, com antecedentes de câncer de mama e neurofibromatose tipo 1, que evoluiu com rápida proptose em olho esquerdo, diagnosticada como sarcoma Mieloide. Os exames subsequentes não demonstraram recidiva da LMA. Essa patologia tem prognóstico indeterminado e sua principal terapêutica é a quimioterapia, embora radioterapia e cirurgia possam ser usadas em casos selecionados.

Palavras-chave: Sarcoma Mieloide; Leucemia Mieloide Aguda; Exoftalmia.

RESUMEN

El sarcoma mieloide es un tumor extramedular macizo, raro, en general asociado a casos de leucemia mieloide aguda (LMA), que puede presentarse en diferentes partes del cuerpo, incluyéndose la órbita. Su diagnóstico es difícil y se realiza sobre todo por los medios anatomopatológico y inmunohistoquímica, ya que los exámenes de imagen carecen de especificidad. El objetivo de este estudio es reportar el caso de una paciente en remisión para LMA, con caso anterior de cáncer de mama y neurofibromatosis tipo 1, que evolucionó con rápida proptosis en el ojo izquierdo, que se diagnosticó como sarcoma mieloide. Los exámenes subsecuentes no reportaron recidiva de la LMA. El pronóstico de esa patología es indeterminado y su principal terapia es la quimioterapia, aunque la radioterapia y la cirugía también sean opciones en casos apartados.

Palabras Clave: Sarcoma Mieloide; Leucemia Mieloide Aguda; Exofalmia.

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INTRODUCTION

Myeloid sarcoma (MS), also known as granulocytic sarcoma or chloroma, is a rare, malignant solid tumor with extramedullary location and is formed by granulocyte precursors (myeloblasts)[1]. It is common in patients with acute myeloid leukemia (AML) but can also be associated with chronic leukemia; myeloproliferative neoplasms, such as polycythemia vera and myelofibrosis; and myelodysplastic syndrome[2].

Any part of the body can be affected by MS; the most common locations include the soft tissues, bones, peritoneum, lymph nodes, skin, kidneys, and gastrointestinal system[13]. Less frequently affected sites include the eye socket, paranasal sinuses, and central nervous system[3].

MS may precede, accompany, or indicate the recurrence of pretreated AML[4]. It is more common in children than in adults[5]. Its appearance in the remission phase of leukemia is a factor for poor prognosis, although cases of good evolution have been reported with early diagnosis and appropriate treatment[21].

Thus, its suspected diagnosis is fundamental and is confirmed using anatomopathological studies and immunohistochemistry. The main treatment approach is usually chemotherapy[19, 27].

Neurofibromatosis type 1 (Von Recklinghausen's disease) is a generally congenital, hereditary, and autosomal dominant disease caused by a mutation in *NF1*[6, 29]. The main clinical signs are *café au lait* spots, dermal and plexiform neurofibromas, axillary and inguinal freckling, and Lisch nodules[12, 28]. Some studies have demonstrated the association of neurofibromatosis type 1 with a higher incidence of some types of cancer, such as breast cancer, as reported in our patient[22, 25].

Although MS is more frequent in other tissues, the importance of ocular involvement should not be overlooked; it has been described in this case report, which addresses the most relevant aspects of the disease that may be useful for its diagnosis and treatment.

CASE REPORT

A 47-year-old Caucasian female visited the Ophthalmology Department of the Redentora Eye Hospital due to hyperemia, pain of moderate intensity, and horizontal diplopia in the left eye, with an evolution period of 2 months (Figure 1). She had a history of neurofibromatosis type 1 diagnosed 32 years ago, left breast cancer treated with total mastectomy and chemotherapy 8 years ago, and AML type M3 (acute promyelocytic leukemia) in remission after chemotherapy and bone marrow transplant from a related donor 5 years ago. There was no significant family history.

Ophthalmological examination showed visual acuity with correction 1.0 for distant vision and J1 for near vision in both the eyes. On ectoscopy, the right eye showed no changes, whereas the left eye showed hyperemia 3+/4+, conjunctival chemosis 4+/4+, palpebral edema 2+/4+, dystopia, and an axial proptosis of 7 mm, which did not increase with the Valsalva maneuver. Extrinsic ocular motility was decreased in the left eye. Biomicroscopy of the anterior segment showed the right eye without changes and left eye with hyperemia, conjunctival chemosis, and mild punctate exposure keratitis. There were no Lisch nodules (iris hamartomas), which are characteristic



Figure 1. Acute proptosis, dystopia, hyperemia and chemosis in the left eye.

of neurofibromatosis type 1. Intraocular pressure was 13 mmHg in the right eye and 18 mmHg in the left eye, and fundoscopy findings and pupil reflexes were within the normal range. General physical examination showed three neurofibromas and six *café au lait* spots distributed on the trunk and limbs as well as axillary freckling due to neurofibromatosis type 1.

Hemogram, evaluation of T3, T4, and TSH (Thyoid Stimulator Hormone) levels, standard chest X-ray examination, and magnetic resonance imaging (MRI) of the brain and orbit were requested, and an oral corticosteroid (prednisone 40 mg/day) and topical ocular treatment were prescribed due to the nonspecific inflammatory process and lubricating drops due to exposure keratitis. On her follow-up visit, the hemogram, thyroid function test results, and chest X-ray findings were unchanged. MRI showed a normal right eye socket and left eye socket with a signal intensity mass similar to the soft parts which were isointense on T1- and hyperintense on T2-weighted images, with homogeneous intra- and extracoronal impregnation enhanced by the paramagnetic agent (gadolinium). The left cavernous sinus was also affected, with compression of the orbital plate and increased thickness of the extrinsic muscles (particularly the medial and inferior rectus muscles), optic nerve involved and with preserved diameter, and eyeball diverted anteriorly with normal sphericity and signal intensity (Figure 2). A lymphoproliferative lesion was suspected, and the patient was referred for biopsy of the lesion.

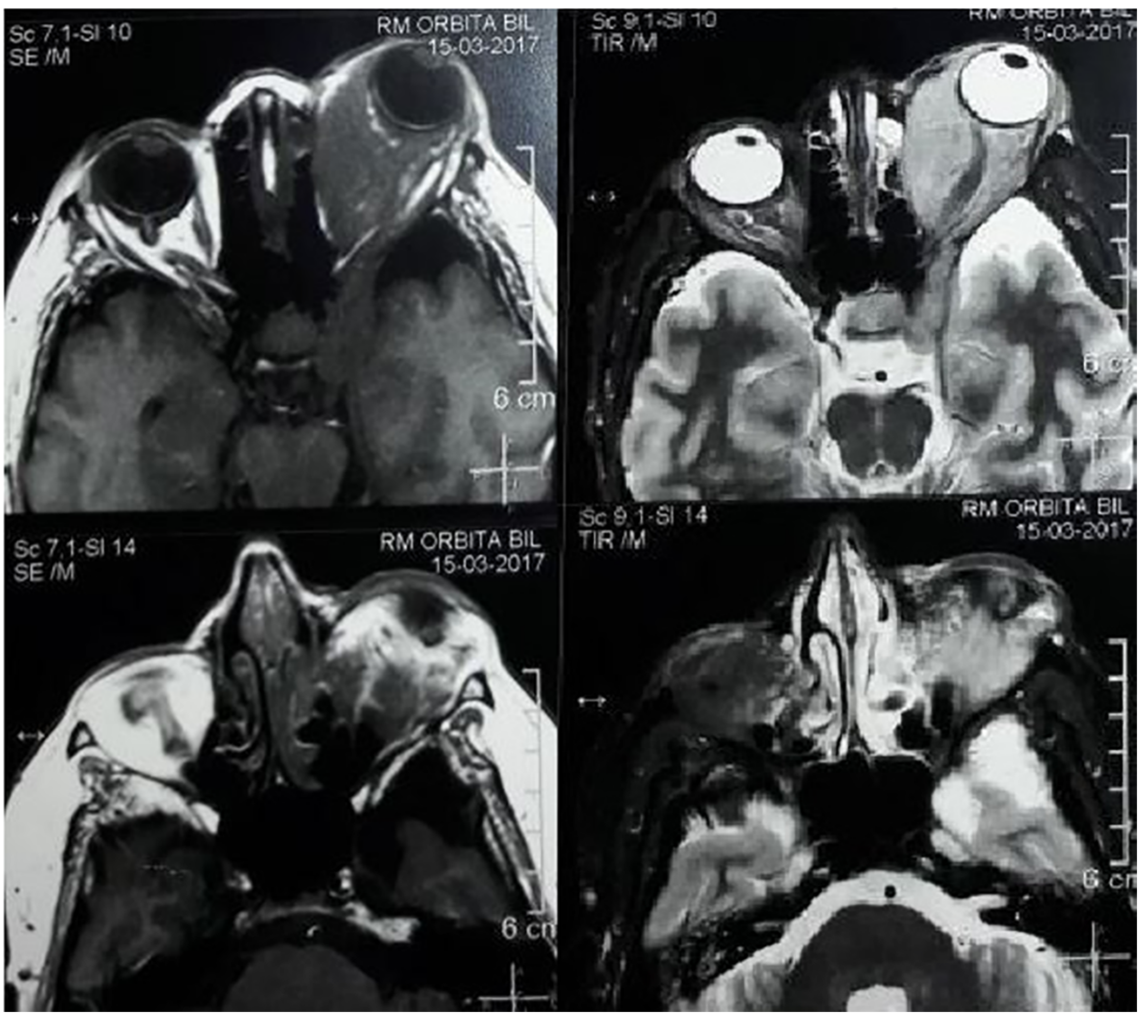


Figure 2. Brain MRI demonstrating the left intraorbital lesion in axial section, isointense in the weighted sequence in T1 and T2-weighted hyperintense, with homogeneous contrast uptake.

The anatomopathological report of the pathology service of the University of São Paulo (USP) in Ribeirão Preto (Serpat-HC) revealed left eye socket infiltration by a hematopoietic neoplasm composed of intermediate-sized neoplastic cells with a high nucleus/cytoplasm ratio, nuclei with irregular borders, moderate-intensity chromatin, immunohistochemically positive for CD117, CD34, myeloperoxidase and negative for CD20, CD3, CD5, CD23, and cyclin D1. MS was therefore diagnosed. A systemic investigation was conducted, including a new hemogram and bone marrow puncture, which showed no bone marrow involvement, thereby ruling out AML recurrence.

We opted for an exclusively chemotherapeutic treatment with three cycles of daunorubicin and cytarabin. The patient responded favorably to treatment, with a marked reduction in proptosis and all the eye conditions by the end of the last chemotherapy cycle (Figure 3).

On follow-up ophthalmological examination at 10 months after the onset of symptoms, the patient had no further complaints and presented no relevant ocular changes. Her corrected visual acuity remained at 1.0 for distant vision and J1 for near vision. Her clinical picture evolved without further complications, and she is now in outpatient follow-up, asymptomatic, and without bone marrow involvement since the start of the eye complaints (11 months ago).

DISCUSSION

MS occurs concomitantly with AML at a rate of 2%–9%[2], either as a single or multifocal tumor; it can occur either in association with other hematological diseases or in isolated form[7]. It is called chloroma due to its typical greenish coloration caused due to the exposure of the enzyme myeloperoxidase to ultraviolet light, although one-third of cases present other colors, such as white, gray, or red, depending on the predominant cells[8]. In most cases, it occurs following the diagnosis of AML but can also occur before or concomitantly with the AML diagnosis or indicate its recurrence in a patient previously treated for this hematological disease[10].

Leukemias are malignancies derived from hematopoietic cells, which proliferate in the bone marrow[24]. Among the several risk factors for AML are chemotherapeutic agents, such as those used in breast cancer, previous radiotherapy, and inherited genetic syndromes, such as neurofibromatosis type 1. AML can lead to the development of extramedullary leukemic cell masses affecting various tissues. Ocular involvement is rare, and changes in the retina and choroid are predominant[9]. The eye socket is rarely involved, and its characteristic symptoms are proptosis, palpebral edema, and chemosis[10].

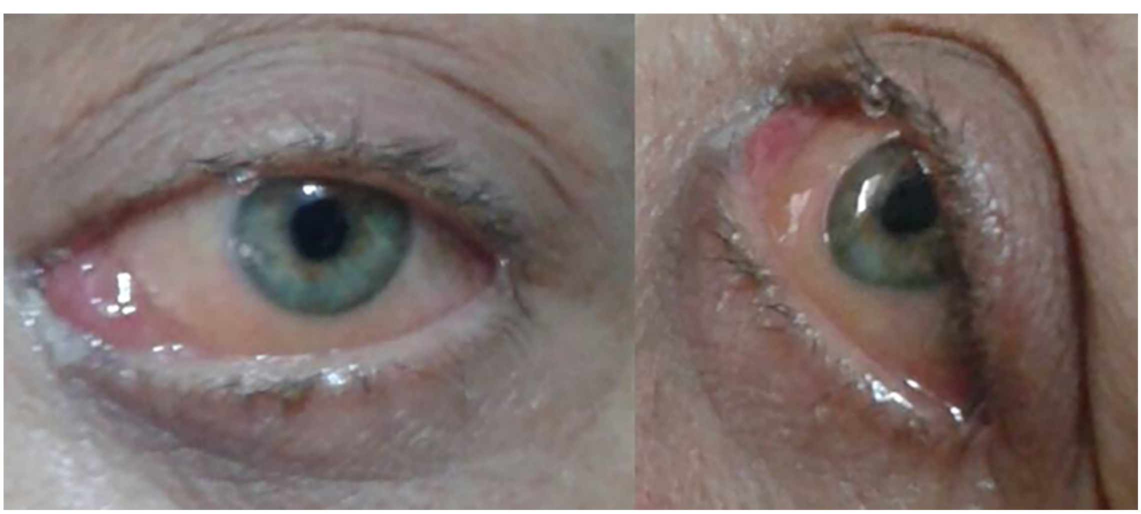


Figure 3. Left eye with marked improvement of proptosis and other ophthalmological signs after the end of chemotherapy.

First described in 1811 by Allen Burns, MS is also known as myeloblastoma, myelocytoma, chloroleukemia, and granulocytic sarcoma. It is composed of immature cells of the granulocytic series, originating from a myeloid precursor, usually myeloblasts[11].

Orbital MS may appear at any age, but it is more common in children with a mean age of approximately 7 years. The disease is rare in adults[10]. It may affect any part of the body; the most common sites include the soft tissues, bones, peritoneum, lymph nodes, skin, kidneys, and gastrointestinal system[13]. Orbital involvement is rare and comprises 10% of orbital tumors along with neoplasms of lymphoid origin[14].

The predilection for bone marrow or subperiosteum involvement in the axial skeleton may be related to increased hematopoiesis in these locations[7], and cases affecting the eye socket can be explained by an origin in the adjacent bone, lacrimal gland, or extraocular muscles[15].

The main signs of ocular involvement are pain, increased volume, involvement of adjacent tissues, inflammation of the eye socket, orbital tumors (palpebral and conjunctival), uveitis, and proptosis, the latter being the most common sign[10.16]. Systemic involvement can vary from 1 to 16 years after the appearance of the orbital lesion[17].

The most commonly used immunohistochemical markers for the diagnosis of MS are positivity for MPO, CD68, CD43, lysozyme, CD45, CD117 (Ckit), CD99, CD33, CD34, and CD13 and negativity for CD3 and CD20[2.19]. The most frequent cytogenetic alterations are similar to those found in AML, such as t(8.21) and inv(16). These changes are often associated with the orbital location of the tumor[18].

The risk factors for the development of MS include cytogenetic abnormalities, such as t (8; 21), inv(16), AML subtypes FAB M4 and M5, increased white blood cells, presence of neural cell adhesion molecules (NCAM), T-cell markers (CD2, CD4, and CD7), poor nutrition, and low socioeconomic level[19]. MS is more common in AML subtypes M2, M4, and M5[19]. Clinical suspicion of this tumor is difficult, and an initial AML presentation in a primarily extramedullary site with unaffected bone marrow and normal hematological findings is very rare[20]. When an orbital tumor is the initial manifestation, peripheral blood and bone marrow usually tend to be involved after 12 months without adequate treatment[10.]

Differential diagnoses for orbital MS include non-Hodgkin lymphoma, rhabdomyosarcoma, anaplastic carcinoma, lymphoblastic leukemia, Ewing sarcoma, eosinophilic granuloma, extramedullary hematopoiesis, melanoma, metastatic neuroblastoma, African Burkitt lymphoma, and idiopathic inflammatory pseudotumor[5].

On computed tomography (CT), MS presents as iso- or hyperdense lesions with uniform contrast uptake[23]. On MRI, the lesions appear as hypo- or isointense on T1 and T2, with homogeneous contrast uptake and a tendency to remain isointense in sequences with a long repetition time (due to the presence of the myeloperoxidase enzyme)[8].

The treatment of orbital MS without systemic involvement is not standardized, and its prognosis is still undetermined. The therapeutic choice for isolated MS is induction chemotherapy used in AML[27]. In MS associated with hematological disease, the treatment is focused on the underlying disease[16]. Some studies have demonstrated the superiority of systemic chemotherapy over local radiotherapy and surgery[27].

Chemotherapy should be started even in cases of MS without bone marrow involvement[19]. Although MS is highly radiosensitive, radiotherapy does not increase the patient's survival rate and is more appropriate in cases of poor response to chemotherapy and recurrence after hematopoietic bone marrow transplant. Surgery is reserved for rapid symptomatic relief, such as when there is compression of adjacent structures causing functional impairment[27].

CONCLUSIONS

Although ophthalmologists have a secondary role in the diagnosis of primary hematological diseases, such as leukemia, their knowledge of these pathologies is of vital importance for the diagnosis of extramedullary diseases that might have more serious consequences to initiate early appropriate treatment.

The objective of this work was to present and discuss the clinical manifestations in a rare case of orbital MS without hematological or bone marrow involvement. Its prognosis has not been established and is highly variable. Early diagnosis and appropriate treatment, which usually includes chemotherapy, are very important.

Therefore, a multidisciplinary approach to MS is needed. Ophthalmologists must pay attention to its atypical clinical manifestations to deal with eye complications at an early stage and avoid systemic involvement.

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